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Signed Andrew Gray

Dated 15 November 1999

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240EC98 E414260 C 002832
P01/7700 0.00 - 9828480.5

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — D079.001.00

2. Patent application number *(The Patent Office will fill in this part)* — **9828480.5** — 24 DEC 1998

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Dermatech Limited
Kramer Mews
London
SW5 9JL

THE PATENT OFFICE
L
24 DEC 1998
RECEIVED BY POST

Patents ADP number *(if you know it)* 7577489001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention

Transdermal Drug Delivery System

5. Name of your agent *(if you have one)*

Serjeants

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

25 The Crescent
King Street
Leicester
LE1 6RX

Patents ADP number *(if you know it)* 0001461001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	4
Claim(s)	
Abstract	
Drawing(s)	1 + 1

10. If you are also filing any of the following, ~~state how many against each item.~~

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	x
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature A C Serjeant Date 23.12.98

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr A C Serjeant
0116 233 2626

Warning

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

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d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

TITLE

Transdermal Drug Delivery Systems

DESCRIPTION

Technical Field

The invention relates to transdermal drug delivery systems, that is systems for the administration of medicine through the skin of a patient. In this way, the medicine avoids passing through the gastro-intestinal tract and liver. Thus metabolism is to some extent avoided, and a smaller dose can be used.

Background Art

GB 2249956 contains a useful summary of the state of the art, and discloses such systems containing super-saturated solutions of an active ingredient within an adhesive layer by use of a carefully selected mixture of solvents.

THE INVENTION

The invention provides a transdermal drug delivery system comprising a pharmaceutically active substance, an adhesive and crotamiton. It has surprisingly been found that crotamiton can act both as a skin penetration enhancer and as a solvent for the active substance. Preferably however, diethyltoluamide also is present as an additional penetration enhancer and solvent. The ratio of crotamiton to diethyltoluamide may be from 5:95 to 95:5% by weight of the total enhancer/solvent content depending on the delivery rate and extent of delivery required for the active substance.

The system is generally presented on a backing sheet and protected up to use by a release liner.

The pharmaceutically active substance may be a hormone such as estradiol, norethisterone acetate, levonorgestrel, ethynodiol diacetate, medroxy progesterone acetate, gestodene or testosterone, an antihypertensive such as

clonidine, a bronchodilatator such as salbutamol or clenbuterol, an anti-tumor agent such as methotrexate 5-fluouracil, an alkaloid such as physostigmine or scopolamine or an analgesic such as fentanyl, sufentanil, buprenorphine or hydromorphone, for example. A system may contain more than one of such pharmaceutically active substances, for example estradiol with norethisterone acetate or with levonorgestrel.

The adhesive can be an acrylate, silicone or polyisobutylene. The active substance is generally incorporated in the solvent/enhancer at room temperature (25°C or below) and in a ratio less than 90% of saturation level to prevent crystal formation during storage. Dissolution may be aided by sonication or warming. The resulting solution can be added slowly to the adhesive which may be in the form of an aqueous dispersion or solution, and mixed. An adhesive thickener may be added to the mixture at about a 50% solution/water mix to produce a thicker spreading solution for reverse roll coating or knife over roll coating.

The resulting delivery system may then be coated onto a release liner, possibly a siliconized polyester or paper, which naturally is impermeable to the active substance. The system can then be dried by circulating hot air, and laminated onto a backing sheet, which may be a 3M Health Care Type 1220, the backing sheet naturally being impermeable to the active substance. The layer may be coated to a wet-coat thickness of from 50 to 500μ. Alternatively, the delivery system mixture may be spread or coated onto the backing sheet, and then laminated to the release liner. The hot air circulation may be effected at gradually increased temperatures from 50°C to 150°C.

DRAWING

Fig. 1 is section through an adhesive tape for application to the skin of a patient comprising a drug delivery system according to the invention. A delivery system comprising an active substance, adhesive and crotamiton as a solvent/skin penetration enhancer 4 is coated as a layer onto a siliconized release paper 2 and laminated onto a backing strip 6.

The following ingredients may be used in the production of delivery systems as described above:

Example 1

	parts by weight
Estradiol Hemihydrate (EP)	1.000
Crotamiton	8.500
Acrylate adhesive (Monsanto 3011)	90.500
Strong ammonia (BP)	qs
Purified water (BP)	qs

Example 2

Estradiol Hemihydrate (EP)	1.000
DEET (USP)	5.600
Crotamiton (USP)	0.560
Acrylate adhesive (Primal N569J)	92.84
Adhesive thickener (Acrysol ASE60)	0.200-0.900
Strong ammonia	qs
Purified water	qs

In-vitro drug delivery through the skin

In-vitro skin permeation experiments with human skin have been on systems made from the above ingredients carried out using Franz-type diffusion cells, and the studies were carried out on a Hanson Microette system.

Dermatomed human skin sections were mounted onto the Franz cells and transdermal drug delivery systems mounted on tape backings (1.5cm^2) were placed on the stratum corneal surface of the skin. Each Franz cell contained 7ml of ethanol phosphate buffered saline as the receptor medium, maintained at 32°C. At predetermined time intervals 0.7ml of the receptor solution was sampled and an equal amount replaced.

The samples were analysed by High Pressure Liquid Chromatography.

Indications

The main indications are in both peri-menopausal and menopausal women for the control in the former of the symptoms of the menopause such as hot flushes, sweating and the other symptoms of the peri-menopause, and in the case of the menopause the prevention of osteoporosis and cardiac events such as coronary thrombosis.

FIG. 1.